Glomerular Permselectivity

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OUTLINE

- Historical perspectives
- Theoretical development
- Experimental and clinical observations
- New directions
- QUIZ TIME!!!

Historical Perspectives

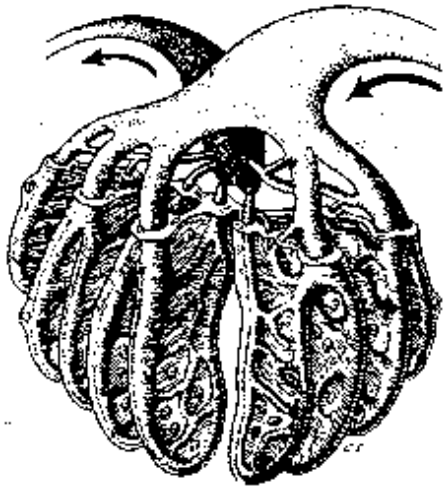
- Brewer, Wallenius (1951, 1954): clearance studies of dextrans in animals
- Pappenheimer, Renkin, *et al.* (1953): first modeling studies of transport through capillary walls
- Hardwicke, Rowe, *et al*. (1955-1961): concepts of “selectivity” of proteinuria and equivalent “pore size”.

Historical Perspecitves (cont.)

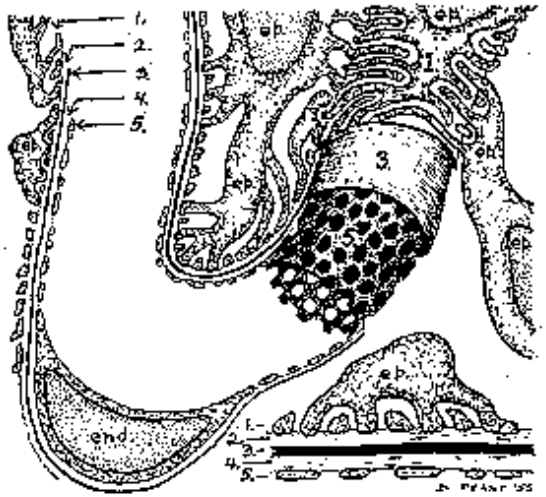
- Chang, Deen, Brenner, *et al.* (1971-1976): spatially dependent models of ultrafiltration and permselectivity with micropuncture studies
- Bohrer, Deen, Rennke, *et al.* (1978-1983): significance of charge-selectivity

How can protein excretion go up as GFR goes down?

- Higher serum concentration
- More filtration from increased convective flow through capillary
- More filtration from increased permeability through capillary
- Less reabsorption or catabolism
- More distal secretion



(a) Anatomy of the glomerular capillary network. Arrows indicate direction of blood flow. From Elias *et al.*[95]



(b) Cross-sectional schematic of the glomerular capillary wall. *end*–endothelial cell, *ep*–epithelial cell. 1–epithelium, 2–lamina rara externa, 3–lamina densa, 4–lamina rara interna, 5–endothelium. From Peaco.[203]

Figure 2-1: Glomerular capillary structure.

Forces which determine GFR

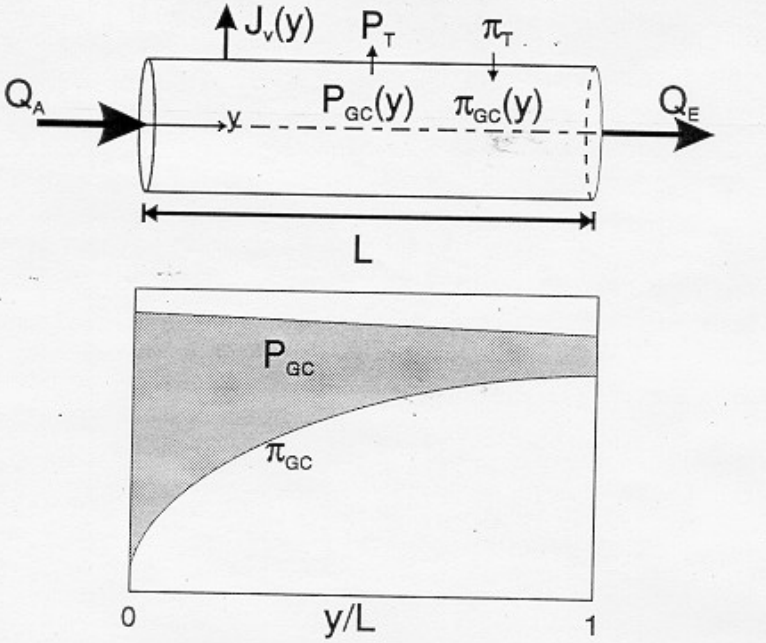


Figure 2-2: Model of glomerular ultrafiltration. *Top*: Afferent (Q_A) and efferent (Q_E) plasma flow is axial in a tube of length L, while solvent flux (J_v) is radial. Hydraulic and osmotic pressures in the capillary (P_{GC}, π_{GC}) vary with position, while those in Bowman's space (P_T, π_T) are constant. Filtration is governed by opposing hydraulic and osmotic pressure differences, resulting in the net flux of solvent (J_v) into Bowman's space. *Bottom*: Hydraulic and osmotic pressure profiles along the length of the glomerular capillary. Hdraulic pressure is nearly constant, while osmotic pressure increases significantly. Shaded area represents the net ultrafiltration driving pressure ($\overline{P}_{UF}$).

Sieving Coefficient

$$\Theta \equiv \frac{\text{Concentration in Bowman's space}}{\text{Concentration in plasma}}$$

$$FC \equiv \frac{\text{urine conc./plasma conc}}{GFR}$$

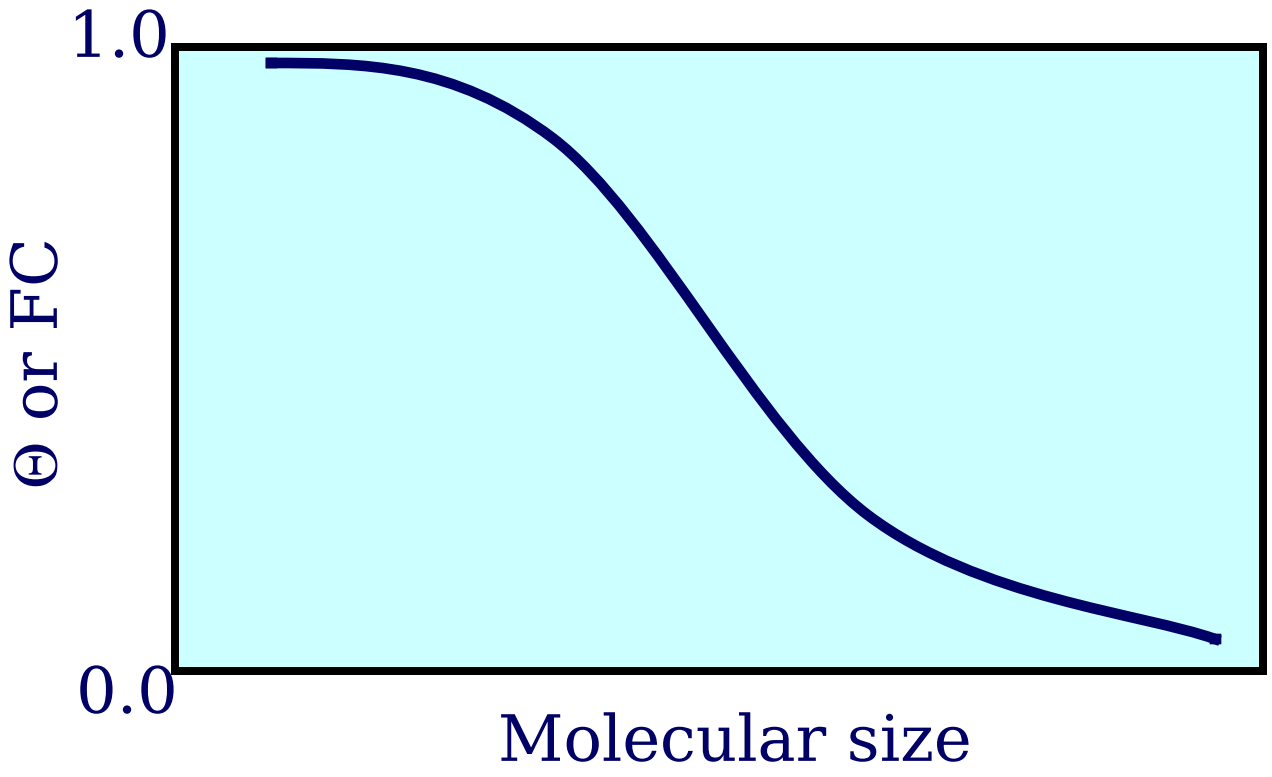
if substance is neither secreted nor reabsorbed

$$\Theta = FC$$

Ideal test molecule

- Neither secreted nor reabsorbed
- Polydisperse in size
- Available with different molecular charges
- Rigid molecular configuration
- Nontoxic

Typical Sieving Data



General Governing Equation

flux=diffusion+convection+ionmigrati

$$J_s = \left[-K_D D_i \frac{dc}{dx} \right] + (K_C J_v c) + \left[-K_D cM \frac{RT}{F} \frac{d\Psi}{dx} \right]$$

Pore model of permselectivity

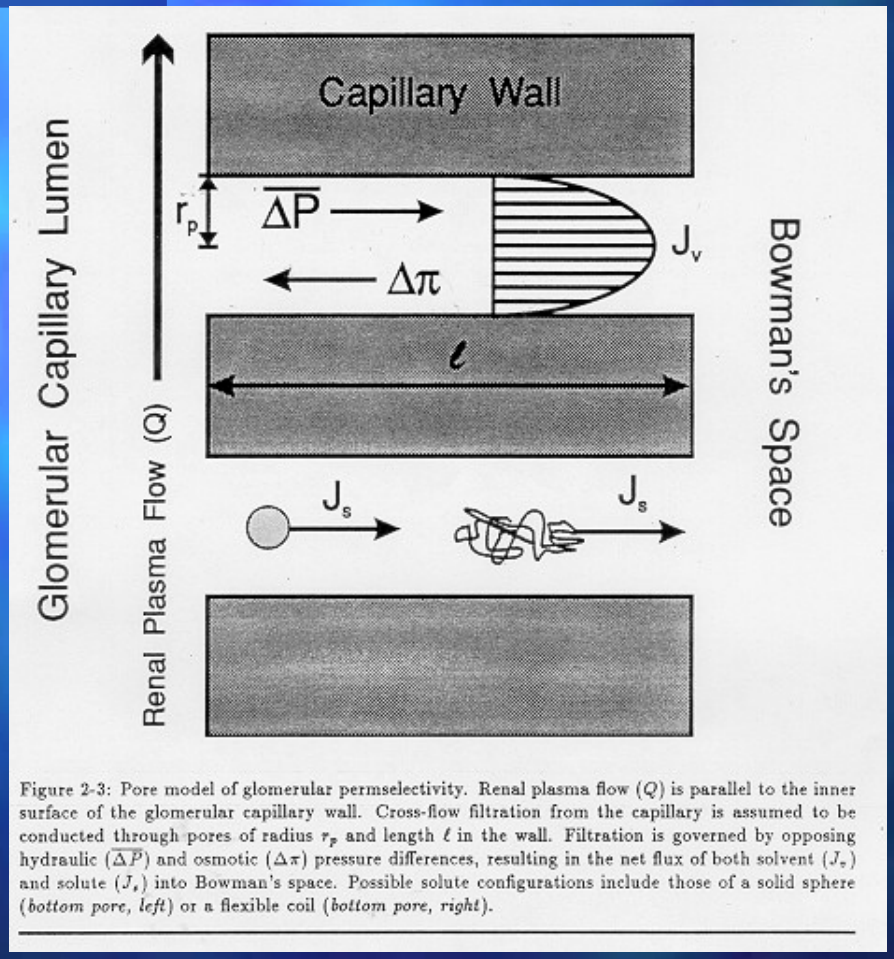
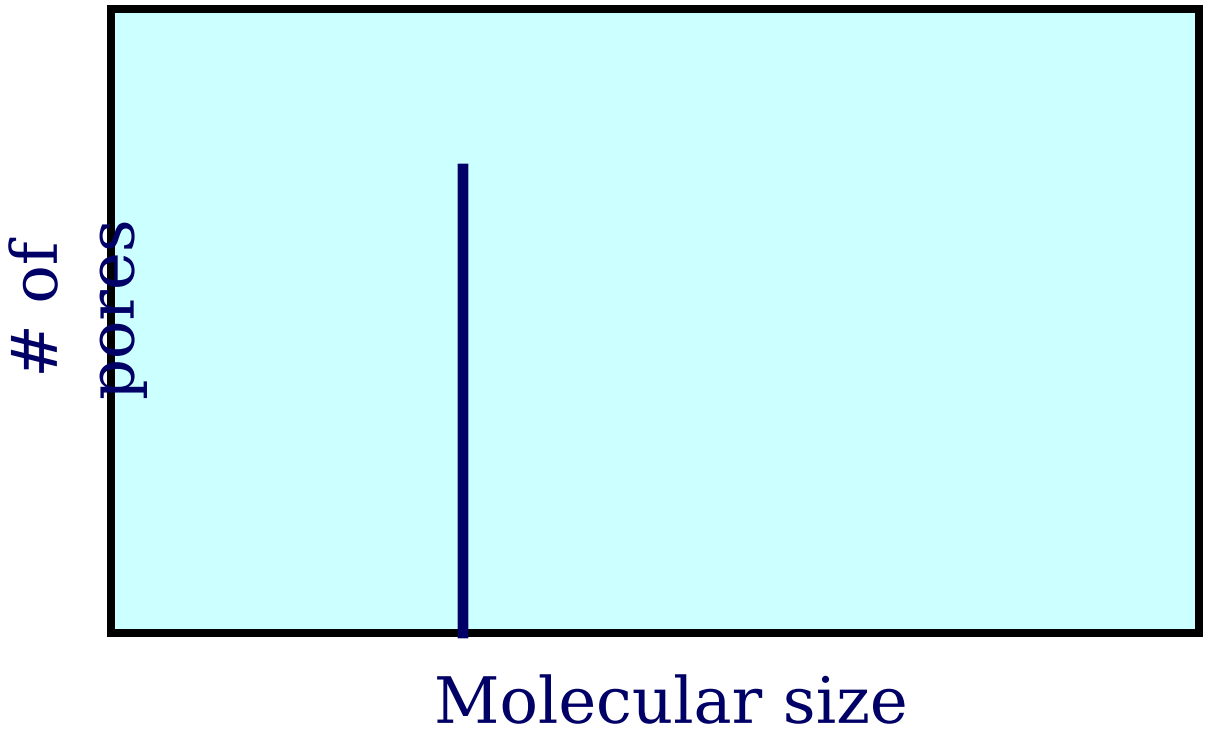
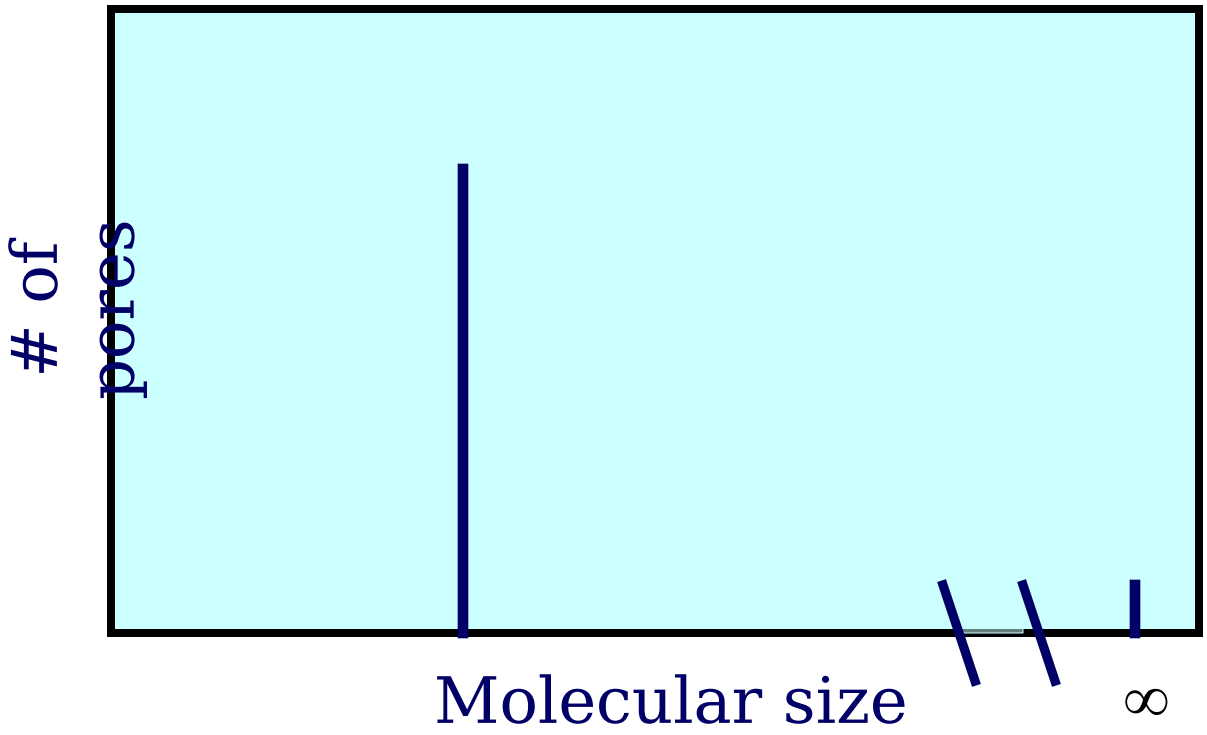


Figure 2-3: Pore model of glomerular permselectivity. Renal plasma flow (Q) is parallel to the inner surface of the glomerular capillary wall. Cross-flow filtration from the capillary is assumed to be conducted through pores of radius r_p and length ℓ in the wall. Filtration is governed by opposing hydraulic ($\overline{\Delta P}$) and osmotic ($\Delta\pi$) pressure differences, resulting in the net flux of both solvent (J_v) and solute (J_s) into Bowman's space. Possible solute configurations include those of a solid sphere (*bottom pore, left*) or a flexible coil (*bottom pore, right*).

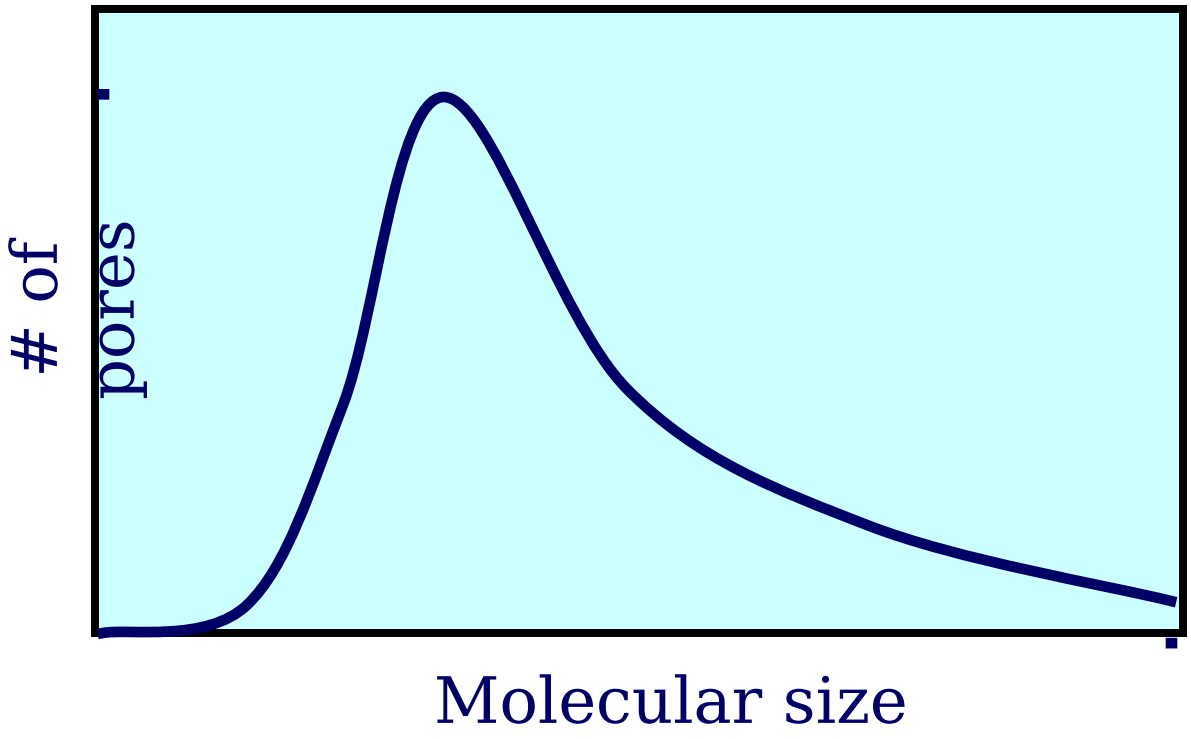
Isoporous Model



Isoporous + shunt model



Lognormal distribution model



Dr. Stiles, your 1:30 walk-in appointment is here to see you . . .

Modeling design

- Model pore-size is a theoretical equivalent, not an anatomical measurement.
- Governing equations are independent of underlying structural model, thus, similar analysis can be done with different (better?) models

Theoretical effect of changes in r_0 and ΔP on sieving curves

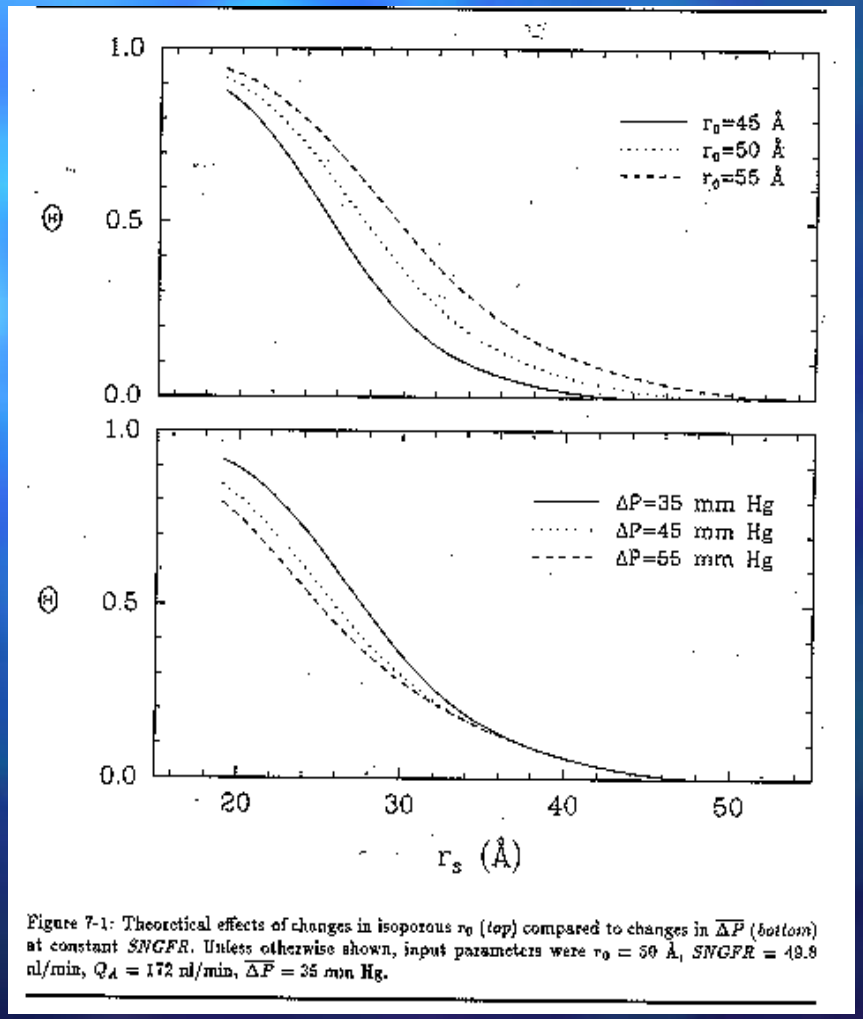


Figure 7-1: Theoretical effects of changes in isoporous r_0 (*top*) compared to changes in $\overline{\Delta P}$ (*bottom*) at constant *SNGFR*. Unless otherwise shown, input parameters were $r_0 = 50$ Å, *SNGFR* = 49.8 nl/min, $Q_A = 172$ nl/min, $\overline{\Delta P} = 35$ *mm* Hg.

Theoretical effects (cont.)

- Increases in r_0 correspond most closely to increases in Θ for large molecules.
- Increases in ΔP correspond most closely to decreases in Θ for small molecules.
- Changes in charge-permselectivity have greatest effect on more heavily-charged and larger molecules
- All things being equal, charge effects tend to be stronger than size effects.

Effect of molecular size and charge

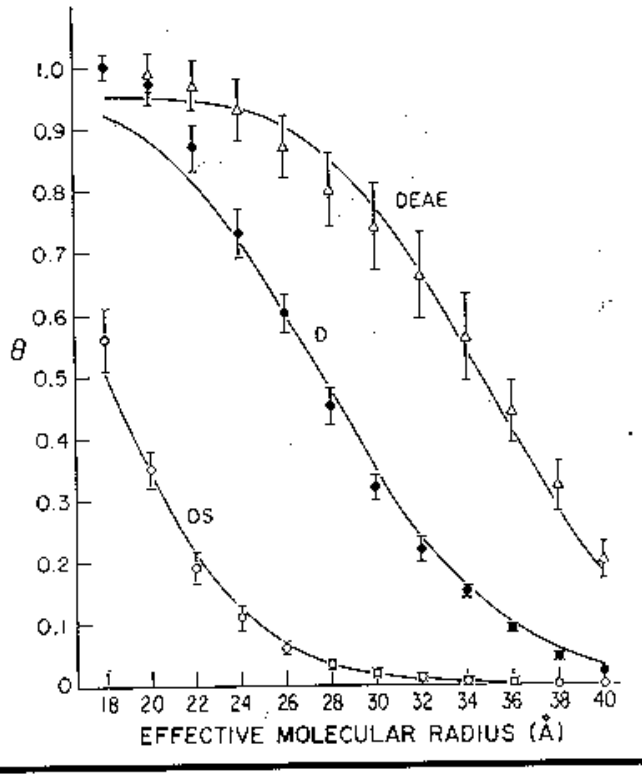
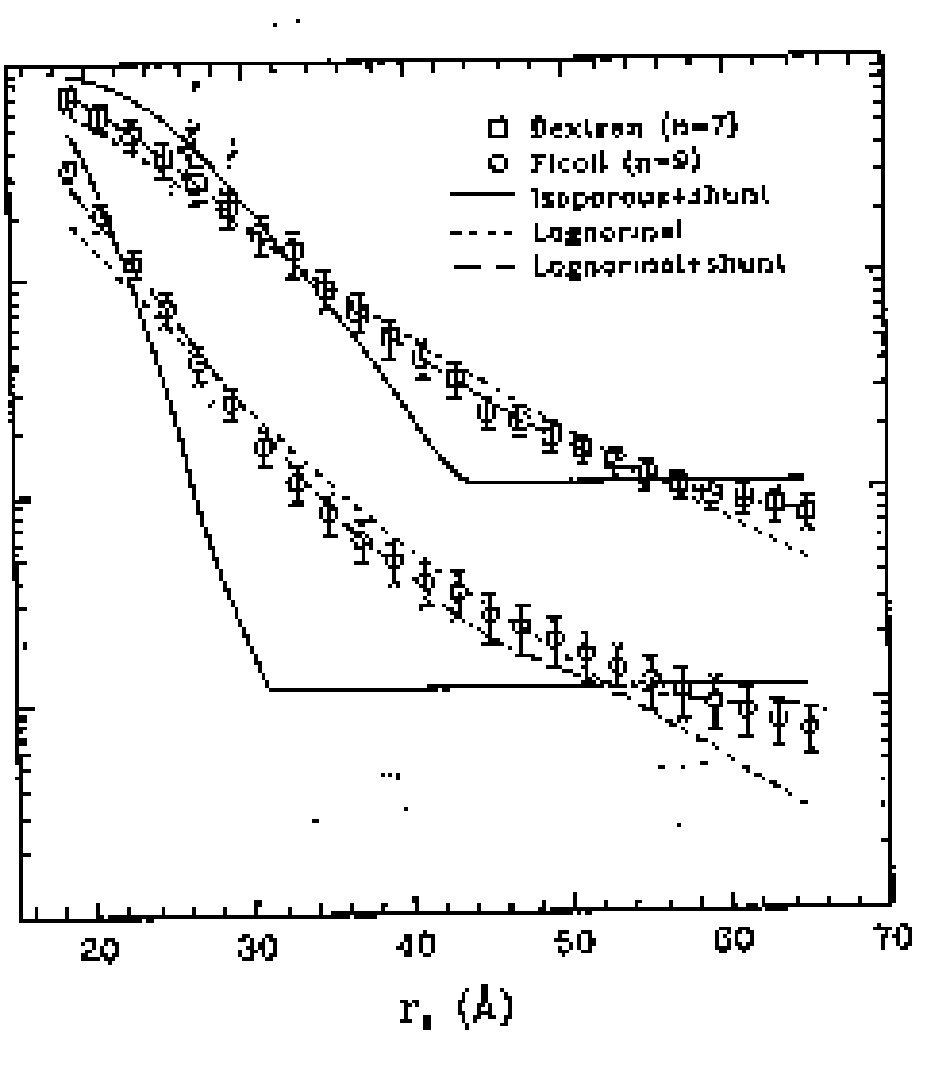


Figure 43–1. Filtrate/plasma concentration ratio (θ) as a function of molecular size for tritiated dextran sulfate (DS), neutral dextran (D), and diethylaminoethyldextran (DEAE). Data points are means ± SE measured in the normal Munich-Wistar rat.[9, 10] All three curves were calculated theoretically by use of the membrane parameters K_f = 4.8 nL/min/mm Hg, r_p = 47 Å, and C_m = 165 mEq/L. (From Deen WM, Satvat B, Jamieson JM: Theoretical model for glomerular filtration of charged solutes. Am J Physiol 238:F126, 1980.)

Effect of molecular configuration



Effect of molecular configuration (cont.)

- Dextran has a sieving coefficient both *in vitro* and *in vivo* which is higher than theoretically predicted.
- Dextran data thus leads one to believe the membrane is less permselective than it actually is.
- Ficoll data corresponds more closely to predicted and observed behavior of proteins.

Effect of molecular configuration (cont.)

	r (A)	Θ
HRP (neutral)	30	0.06
Ficoll	30	0.02
dextran	30	0.19
albumin	36	0.0003
Ficoll	36	0.008
dextran	36	0.08

Effect of disease

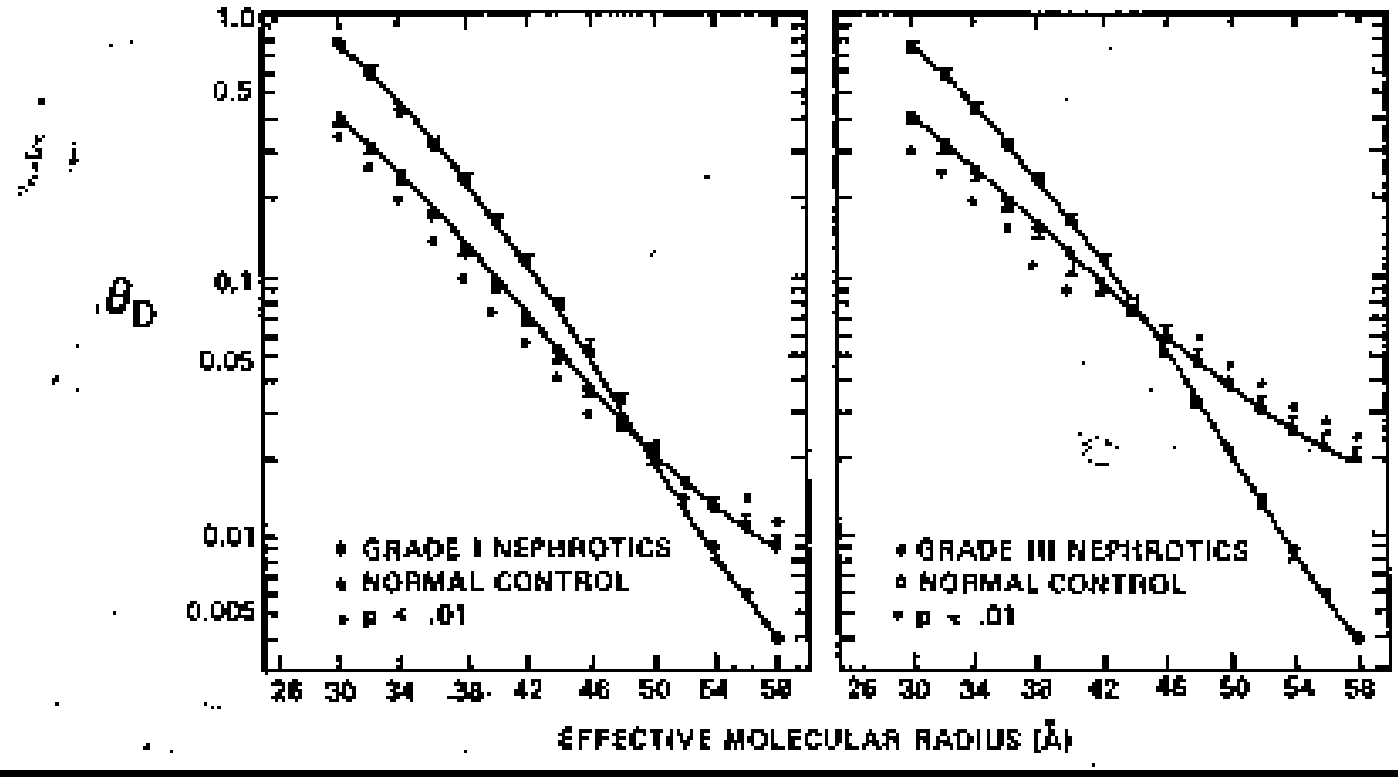


Figure 43-2. Fractional dextran clearances (θ_D) plotted as a function of molecular radius. Grade I (*left*) and grade III (*right*) nephrotic patients are compared with normal control subjects. Values are means ± SE. (From Deen WM, Bridges CR, Brenner BM, Myers BD: Heteroporous model of glomerular size selectivity: Application to normal and nephrotic humans. Am J Physiol 249:F374, 1985.)

General trends seen in disease

- Θ increases for large molecular size (increase in r_0).
- Θ decreases for small molecular size (increase in ΔP).
- Variable losses in charge-selectivity.
- K_f decreases.

Have a cookie, Dr. LeBrun, the P.T. test is still several weeks away . . .

Results from pore size modeling

- r_0 ~ 45-55 angstroms under normal circumstances
- In disease states r_0 usually increases slightly. Major change is seen in fraction of large pores ("shunt fraction").

Anatomical Basis of Permselectivity

- Cells vs. GBM: cells give most of the permselectivity from *in vitro* studies.
- Endothelial fenestrae provide little to no barrier.
- Slit diaphragms are probably most important site of size-selectivity.

Anatomical Basis of Permselectivity (cont.)

- GBM and epithelial cells contain many negatively-charged macromolecules, especially heparan sulfate, which imparts charge-selectivity.

Physiological modulators of permselectivity

- Angiotensin II
- ΔP
- Neurohormones
- Plasma volume expansion
- Dietary protein intake
- Ca^{++}-channel blockade

Limitations of current theory

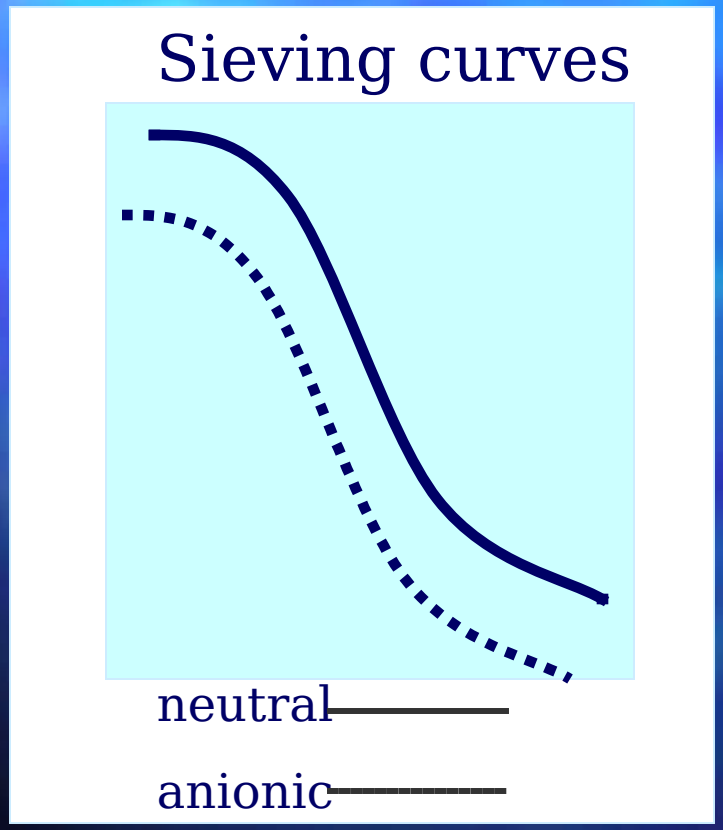
- Lack of correlation to specific glomerular ultrastructure.
- Does not take into account possible active cellular mechanisms.
- Does not account for changes in proximal tubule reabsorption
- Limited quantitative correlation of test molecule clearances to protein secretion

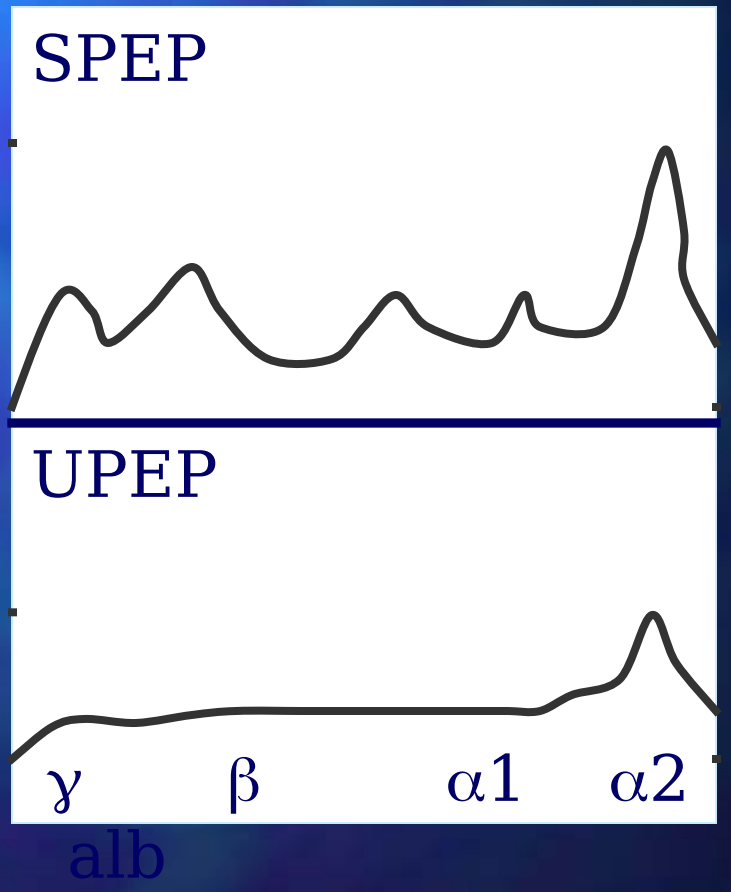
Current and future directions

- Development of mathematical models with incorporation of actual glomerular ultrastructure
- Use of in vitro model to elucidate determinants of permselectivity
- Clinical use of test molecules with anionic charge (Ficoll sulfate?)

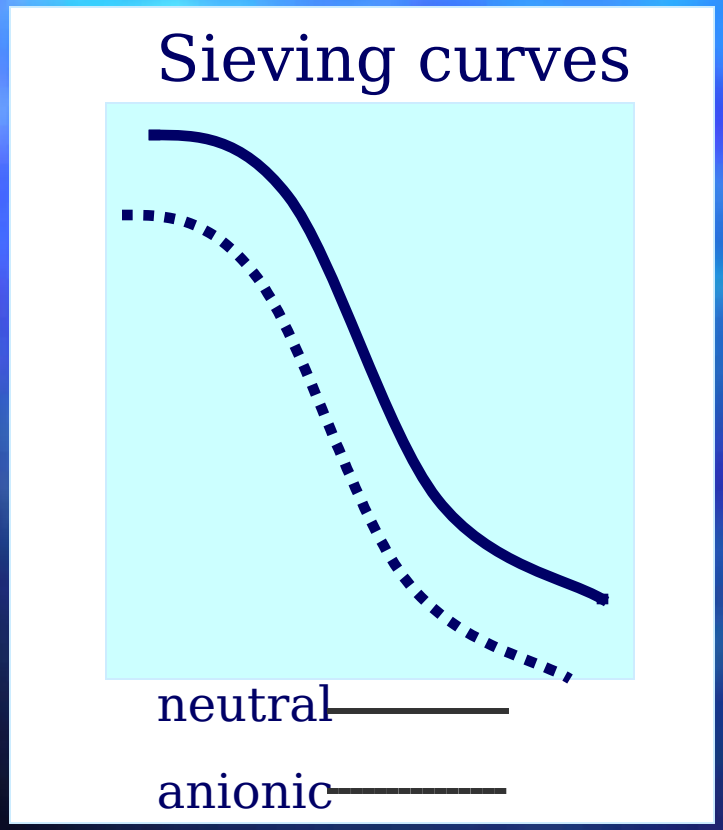
Okay, folks, it’s time for the QUIZ!!!!

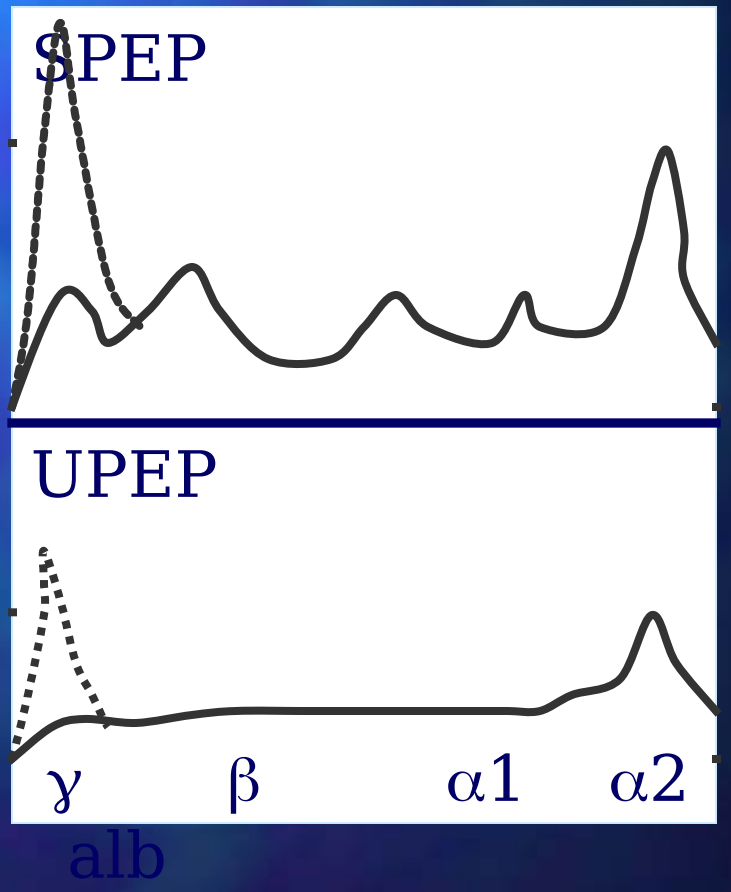
Clinical Scenario 1: Normal Filtration Barrier



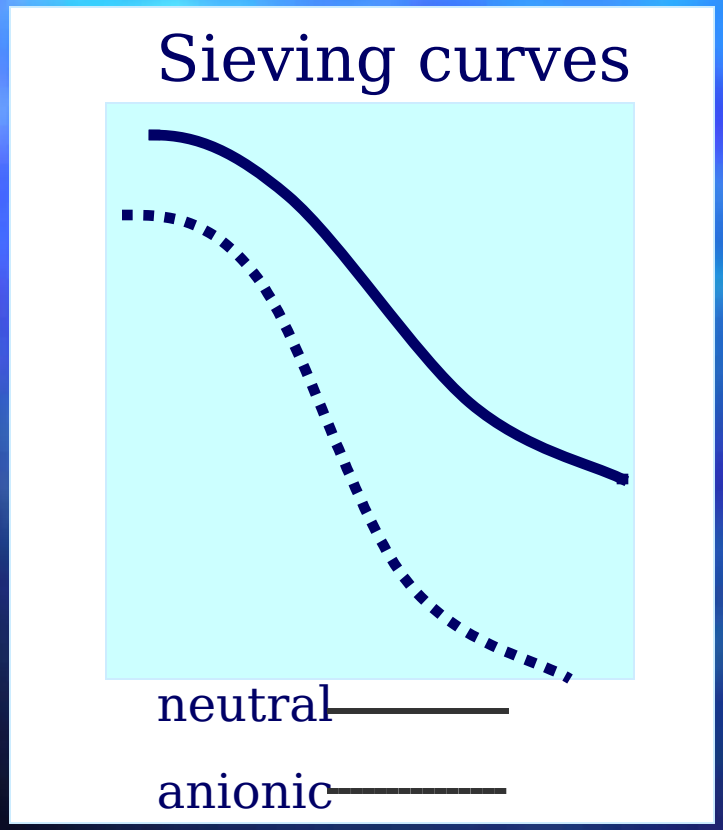


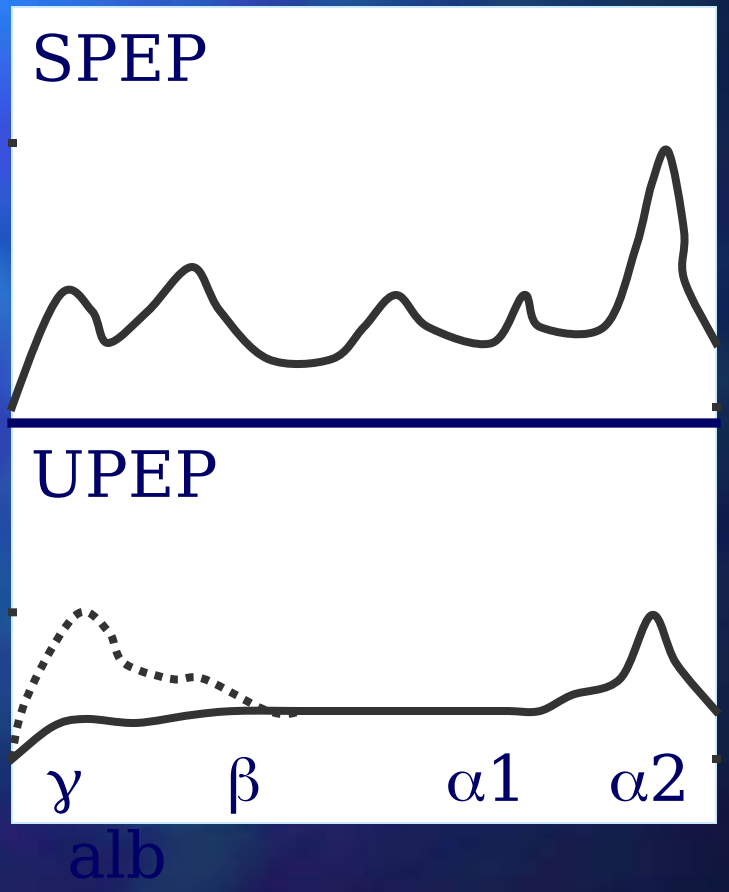
Clinical Scenario 2: Increased Serum Proteins



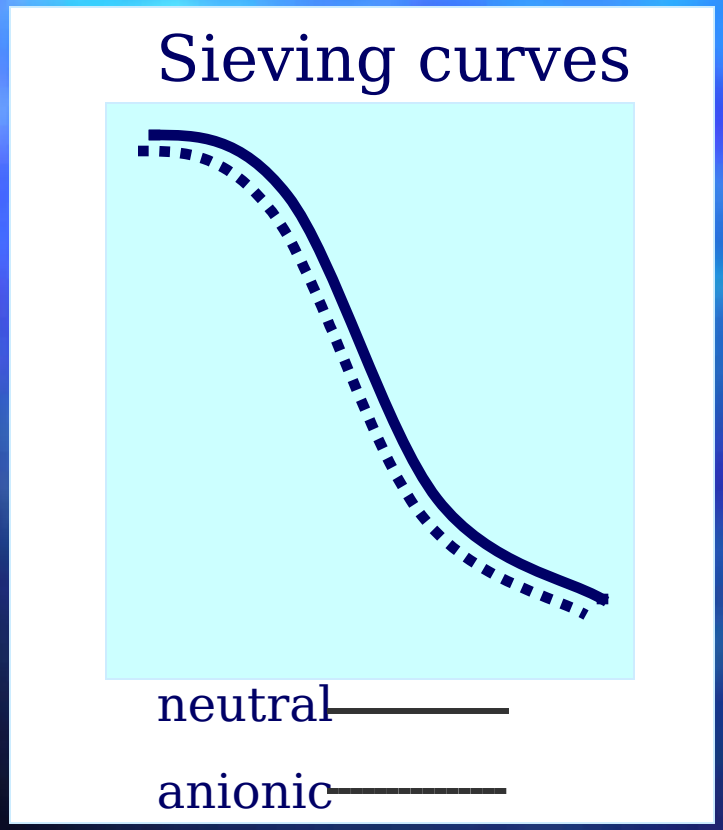


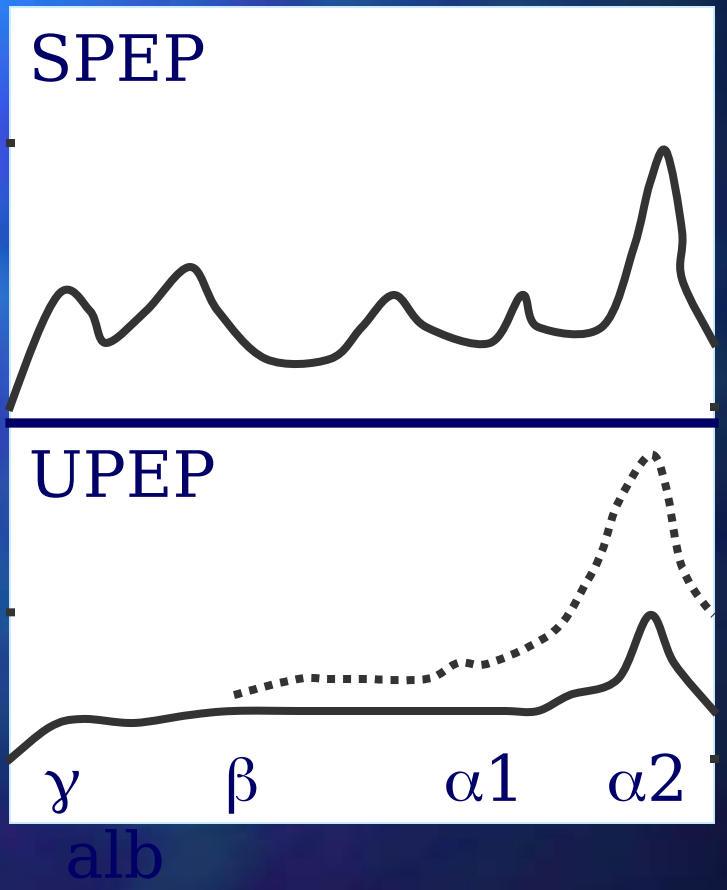
Clinical Scenario 3: Isolated Loss of Size-Selectivity



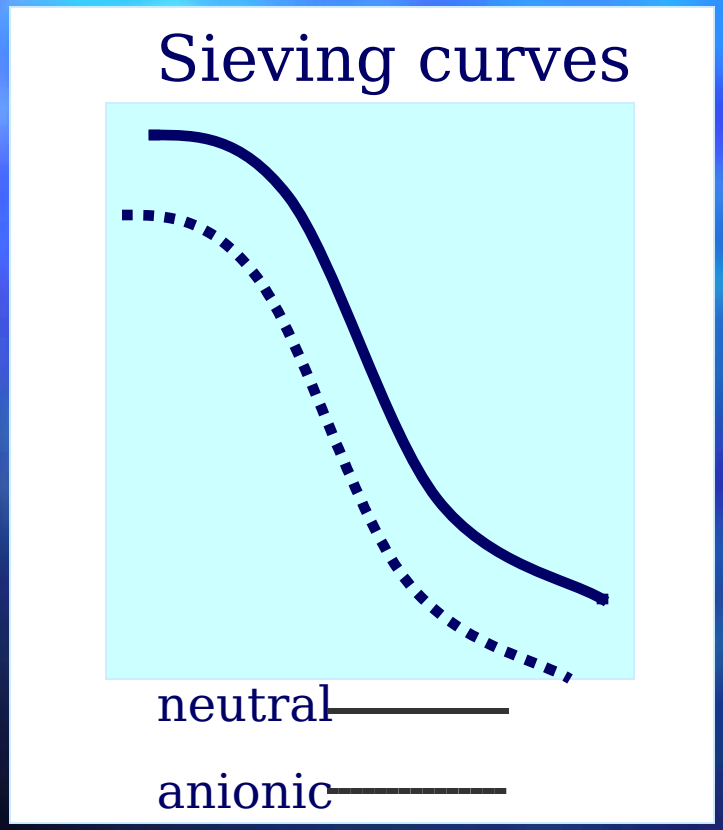


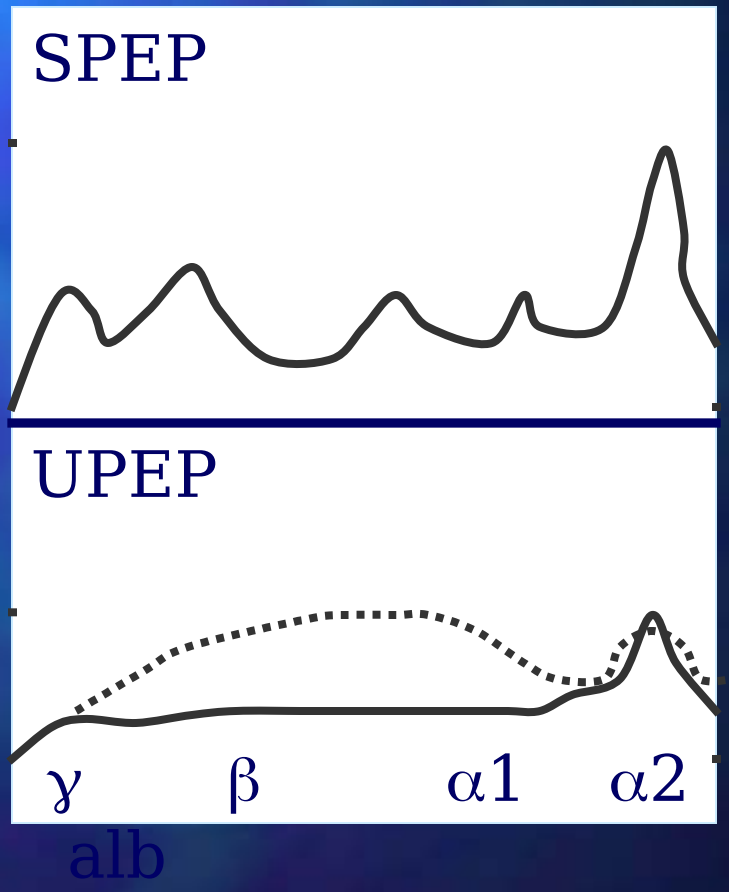
Clinical Scenario 4: Loss of Charge-Selectivity





Clinical Scenario 5: Defect in Tubular Reabosorption





THE END

A WRAMC Nephrology Fellowship Presentation